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GENE REGULATION IN CELL MODELS OF HUNTINGTON'S DISEASE: A REVIEW

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ABSTRACT

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by expansion of CAG trinucleotide repeats in the Huntingtin (HTT) gene. The mutation results in production of mutant huntingtin protein (mHTT), leading to progressive neuronal dysfunction and degeneration. Although the genetic cause of HD has been well established, the molecular mechanisms responsible for neuronal death remain complex. Recent investigations have demonstrated that transcriptional deregulation, altered microRNA expression, mitochondrial dysfunction, apoptosis, and defective autophagy are central events in HD pathogenesis. Cell-based models have become valuable tools for understanding these molecular abnormalities because they permit controlled investigation of gene regulation and signaling pathways. This review summarizes current knowledge regarding gene regulatory mechanisms in Huntington's disease, emphasizing transcription factors, microRNAs, mitochondrial regulators, and co-expression networks that contribute to disease progression. Understanding these mechanisms may facilitate the development of novel therapeutic strategies targeting gene expression pathways.

KEYWORDS: Huntington's disease, Huntingtin, Gene regulation, MicroRNA-214, E2F1, MFN2, Mitochondria, Neurodegeneration.

INTRODUCTION

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric abnormalities. The disease

results from expansion of CAG repeats beyond the normal range in exon 1 of the HTT gene, producing an abnormally long polyglutamine tract within the huntingtin protein. Progressive accumulation of mutant huntingtin disrupts numerous cellular pathways including transcription, protein degradation, mitochondrial function, and intracellular signaling.

Although mutant huntingtin is expressed throughout the body, neuronal populations within the striatum and cerebral cortex exhibit remarkable vulnerability. Modern molecular studies have demonstrated that neuronal degeneration is not solely caused by toxic protein aggregation but also by widespread alterations in gene expression. Consequently, understanding transcriptional and post-transcriptional regulation has become a major area of Huntington's disease research.

Cell models expressing either wild-type or mutant huntingtin provide experimental systems for examining these regulatory mechanisms under controlled laboratory conditions.

Molecular Mechanisms of Gene Regulation in Huntington's Disease

One of the major pathological features of Huntington's disease is extensive transcriptional deregulation. Mutant huntingtin interferes with multiple transcription factors and chromatin-modifying proteins, leading to altered expression of hundreds of genes involved in neuronal survival.

Wild-type huntingtin normally participates in transcriptional regulation, intracellular transport, autophagy, and mitochondrial maintenance. However, expansion of polyglutamine repeats alters protein conformation, resulting in abnormal protein-protein interactions and sequestration of transcription factors.

Genome-wide analyses have demonstrated that numerous genes become either upregulated or downregulated during disease progression. These genes participate in biological processes including:

- Apoptosis
- Cell cycle regulation
- DNA repair
- Protein degradation
- Synaptic transmission
- Oxidative stress response
- Energy metabolism
- Mitochondrial function

Such widespread transcriptional changes contribute significantly to neuronal dysfunction and

disease progression.

Role of Co-expression Networks

Gene co-expression network analysis has emerged as an effective strategy for identifying genes that function together within biological pathways. Studies have identified more than 200 genes co-expressed with wild-type HTT. Many of these genes are directly associated with Huntington's disease pathology.

Co-expression analysis suggests that these genes share common transcriptional regulators and participate in interconnected biological pathways. Network analysis has demonstrated enrichment of genes involved in:

- Protein homeostasis
- RNA processing
- Cell cycle regulation
- Mitochondrial organization
- Autophagy
- DNA damage response

Because co-expressed genes frequently participate in similar cellular functions, these networks provide valuable insight into disease mechanisms and potential therapeutic targets.

MicroRNA-Mediated Regulation

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by binding messenger RNA and inhibiting translation or promoting degradation.

Among several dysregulated miRNAs in Huntington's disease, miR-214 has attracted considerable attention. Experimental evidence indicates that miR-214 regulates multiple genes involved in mitochondrial dynamics and neuronal survival.

One important target is Mitofusin-2 (MFN2), a mitochondrial membrane protein essential for mitochondrial fusion. Increased expression of miR-214 reduces MFN2 expression, resulting in fragmented mitochondria and impaired cellular energy metabolism.

Besides MFN2, miR-214 influences genes involved in:

- Cell proliferation
- DNA repair
- Apoptosis
- Cell cycle progression

- Autophagy

These observations suggest that abnormal miRNA expression contributes substantially to Huntington's disease pathology.

Transcription Factors in Huntington's Disease

Transcription factors coordinate expression of numerous genes simultaneously. Several transcription factors exhibit altered activity in Huntington's disease.

Among them, **E2F1** and **SP1** play important regulatory roles.

Experimental studies demonstrate that E2F1 activates MFN2 transcription by binding its promoter. SP1 cooperates with E2F1 to maintain normal mitochondrial gene expression.

Disruption of these regulatory pathways causes:

- Reduced mitochondrial biogenesis
- Increased oxidative stress
- Impaired mitophagy
- Altered neuronal metabolism
- Enhanced apoptosis

Other transcription factors implicated include TP53, REST, NF-κB, CREB, and ETS1, all of which regulate genes essential for neuronal function and survival.

Mitochondrial Dysfunction and Neurodegeneration

Mitochondrial dysfunction is recognized as one of the earliest pathological events in Huntington's disease.

Mutant huntingtin impairs mitochondrial transport, ATP production, calcium homeostasis, and oxidative phosphorylation. Fragmentation of mitochondria further increases oxidative stress and activates apoptotic pathways.

Reduced MFN2 expression contributes to defective mitochondrial fusion and abnormal mitochondrial morphology.

Experimental studies demonstrate that restoration of MFN2 expression partially rescues mitochondrial defects, highlighting its therapeutic potential.

Therapeutic Perspectives

Understanding gene regulation has opened several promising therapeutic approaches. Potential interventions include:

- Gene silencing using antisense oligonucleotides
- RNA interference
- MicroRNA modulation
- CRISPR-based genome editing
- Small molecules targeting transcription factors
- Epigenetic therapy
- Mitochondrial protective agents

These strategies aim to reduce mutant huntingtin toxicity while preserving normal HTT function.

Although several treatments remain experimental, advances in molecular biology continue to improve prospects for disease-modifying therapies.

CONCLUSION

Gene regulation plays a central role in Huntington's disease pathogenesis. Altered transcription factor activity, dysregulated microRNAs, impaired mitochondrial dynamics, and disrupted gene co-expression networks collectively contribute to neuronal degeneration. Cell models have greatly enhanced understanding of these molecular mechanisms by providing experimental systems for investigating gene function and regulatory pathways.

The identification of regulatory molecules such as miR-214, E2F1, and MFN2 offers promising therapeutic opportunities. Future research integrating genomics, transcriptomics, and targeted molecular therapies is expected to improve treatment strategies and slow disease progression.

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